PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 32980/PC/LA	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/SI 03/00045	International filing date *(day/month/year)* 11.12.2003	Priority date *(day/month/year)* 17.12.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/435		
Applicant LEK PHARMACEUTICALS D.D. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 3 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09.06.2004	24.03.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Paul Soto, R Telephone No. +49 89 2399-7346

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/SI 03/00045

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-26 as originally filed

Claims, Numbers

1-14 received on 25.10.2004 with letter of 22.10.2004

Drawings, Sheets

1/3-3/3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-11, 14
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-11, 14
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-14
	No:	Claims	

2. Citations and explanations

   see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Reference is made to the following documents:

D1: MILIVOJEVIC N ET AL: "A novel ergoline derivative LEK-8829 attenuates cocaine-induced reinstatement of cocaine-seeking behavior." BEHAVIOURAL PHARMACOLOGY, vol. 14, no. Supplement 1, September 2003 (2003-09), page S55, XP009029779 10th Biennial Meeting of the European Behavioural Pharmacology Society;Antwerp, Belgium; September 06-09, 2003;

D2: GLAVAN GORDANA ET AL: "Modulation of neuroleptic activity of 9,10-didehydro-N-methyl-(2-prop ynyl)-6-methyl-8-aminomethylergoline bimaleinate (LEK-8829) by D1 intrinsic activity in hemi-parkinsonian rats." MOLECULAR PHARMACOLOGY. UNITED STATES FEB 2002, vol. 61, no. 2, February 2002 (2002-02), pages 360-368, XP002277656;

D3: ZIVIN M ET AL: "Antiparkinsonian potential of interaction of LEK-8829 with bromocriptine." EUROPEAN JOURNAL OF PHARMACOLOGY. NETHERLANDS 22 MAY 1998, vol. 349, no. 2-3, 22 May 1998 (1998-05-22), pages 151-157, XP002277657;

D4: US-A-4 935 429 (DACKIS CHARLES A ET AL) 19 June 1990;

D5: WO 01/41763 A (BERGER STEPHEN PAUL ;UNIV CINCINNATI (US)) 14 June 2001;

D6: US-A-5 441 961 (COHEN MARLENE L ET AL) 15 August 1995;

D7: US-A-5 430 031 (BRAMBILLA ENZO ET AL) 4 July 1995;

If not indicated otherwise, the relevant passages are those mentioned in the International Search Report.

2. The present application according to **claim 1** relates to the use of the therapeutic amount of 9,10-didehydro-N-methyl-N-(2-propynyl)-6-methyl-8β-aminomethylergoline as a partial agonist in the form of a free base or a pharmaceutically acceptable acid addition salt for the manufacture of a medicament for the treatment of psychostimulant addiction in humans. **Claim 6** relates to the use of the therapeutic amount of 9,10-didehydro-N-methyl-N-(2-propynyl)-6-methyl-8β-aminomethylergoline in the form of a free base or a pharmaceutically acceptable acid addition salt for the manufacture of a

medicament for the treatment of cocaine addiction in humans. **Claim 12** relates to a pharmaceutical composition comprising from 0.05 to 20 mg of said agent, wherein the pharmaceutical composition is used for the treatment of cocaine addiction in cocaine addicts. Finally, **claims 5** and **14** are drafted as independent claims but appear to cover the same scope as independent claims 1 and 6, respectively (see item VIII).

3.1. The present application does not meet the requirements of the PCT with respect to novelty (Art. 33) for the following reasons.

The compound LEK-8829 has been already disclosed in the art as pharmaceutical agent (see for example **D2** and **D3**). Thus, **claims 12** and **13**, directed to a pharmaceutical composition are not novel. The technical feature of "wherein said pharmaceutical composition is used for the treatment of cocaine addiction in cocaine addicts" does not limit in any way the scope of present claims 12 and 13, because they are directed to a pharmaceutical preparation and a pharmaceutical preparation is defined by its components, in this case LEK-8829, and not by the medical indication intended for it.

3.2. The subject-matter of present claims 1-11 and 14 is novel, because none of the documents of the prior art discloses the compound referred to as LEK 8829 in connection with the treatment of psychostimulant addiction. **D1** would be novelty destroying for the present application if the priority was not valid.

4. Present claims 1-11 and 14 also meet the requirements of inventive step (Art. 33(3) PCT). Several documents of the prior art disclose ergoline derivatives for the treatment of psychostimulant abuse (see **D4-D7**). **D4**, which can be regarded as the closest prior art, discloses the use of bromocriptine for the treatment of addiction to cocaine and other psychostimulants. The present application differs from **D4** in that another ergoline derivative is used. The use of LEK-8829 exhibits some advantages with regard to the known bromocriptine (see second paragraph in page 6, the examples and the results and conclusion on pages 20-24 of the description).

Thus, the *problem* to be solved by the present application can be regarded as the provision of an ergoline derivative for an improved treatment of psychostimulant addiction. The *solution* provided by the present application, namely the use of LEK 8829 is not rendered obvious by any prior art documents, either alone or in combination.

Some documents, such as **D3**, disclose comparative examples with LEK-8829 and bromocriptine. However, even if LEK-8829 was to be regarded as an obvious alternative to bromocriptine, the advantages exhibited by LEK-8829 in connection with the treatment of psychostimulant addiction could not be foreseen by the skilled person.

5.1. For the assessment of the present claims 1-11 and 14 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

5.2. Claims 12-13 meet the criterion set forth in Article 33(4) PCT because their subject-matter is susceptible of industrial application.

Re Item VIII
Certain observations on the international application

6. The formulation of present independent claims 1 and 6 includes some differences with respect to that of claims 5 and 14, respectively, namely "the therapeutically effective amount of", "as a partial agonist", "in humans". However, it is not clear (Art. 6 PCT) whether these differences represent a limitation on the scope of said claims or not; and if so, which limitations. As far as this is not clear, the scope of claims 1 and 5 on one hand, and claim 6 and 14 on the other hand, is considered to be identical, and therefore the claims are redundant.

CLAIMS

1. A method for the treatment of psychostimulant addiction in humans characterized in that the individuals requiring said treatment are administered the therapeutically effective amount of 9,10-didehydro-N-methyl-N-(2-propynyl)-6-methyl-8ß-aminomethylergoline as a partial dopamine agonist in the form of free base or in the form of pharmaceutically acceptable acid addition salt which inhibit psychostimulant addiction.

2. The method according to claim 1 for inhibition or elimination of the abstinence symptoms due to withdrawal of a psychostimulant with 9,10-didehydro-N-methyl-N-(2-propynyl)-6-methyl-8ß- aminomethylergoline in the form of a simple base or in the form of pharmaceutically acceptable acid addition salt, in the individuals requiring said treatment, in the therapeutically effective amount to suppress the abstinence syndrome after withdrawal of the psychostimulant.

3. The method according to claim 1 for prevention of craving for the psychostimulant after its withdrawal by using 9,10-didehydro-N-methyl-N-(2-propynyl)-6-methyl-8ß-aminomethylergoline in the form of free base or in the form of pharmaceutically acceptable acid addition salt, in the individuals requiring said treatment, in the therapeutically effective amount to suppress the symptoms of craving for the psychostimulant reinforcement.

4. The method according to any of claims 1 to 3, wherein the psychostimulant is selected from the group comprising cocaine, amphetamine, methamphetamine, dextroamphetamine, 3,4-methylenedioxymethamphetamine and pemoline in the form of free base or in the form of a pharmaceutically acceptable acid addition salt.

5. The use of 9,10-didehydro-N-methyl-N-(2-propynyl)-6-methyl-8ß-aminomethyllergoline in the form of free base or in the form of pharmaceutically acceptable acid addition salt for the preparation of the pharmaceutical composition for the treatment of psychostimulant addiction.

6. A method of treatment of cocaine addiction in humans wherein the individuals requiring said treatment are administered the therapeutically effective amount of 9,10-didehydro-N-methyl-N-(2-propynyl)-6-methyl-8ß-aminomethyllergoline in the form of free base or in the form of pharmaceutically acceptable acid addition salt to suppress cocaine addiction.

7. The method according to claim 6 characterized for inhibition or elimination the abstinence symptoms due to cocaine withdrawal using 9,10-didehydro-N-methyl-N-(2-propynyl)-6-methyl-8ß-aminomethylergoline in the form of free base or in the form of pharmaceutically acceptable acid addition salt in the individuals requiring said treatment in the therapeutically effective amount to reduce the abstinence syndrome after cocaine withdrawal.

8. The method according to claim 6 for prevention of cocaine-seeking after its withdrawal using 9, 10-didehydro-N-methyl-N-(2-propynyl)-6-methyl-8ß-aminomethylergoline in the form of free base or in the form of pharmaceutically acceptable acid addition salt in the individuals requiring said treatment in the therapeutically effective amount to suppress the symptoms of craving for the psychostimulant reinforcement.

9. The method according to any of claims 6 to 8 wherein 9,10-didehydro-N-methyl-N-(2-propynyl)-6-methyl-8ß-aminomethylergoline is in the form of bimaleate salt.

10. The method according to any of claims 6 to 9 wherein the daily dose of 9,10-didehydro-N-methyl-N-(2-propynyl)-6-methyl-8ß-aminomethylergoline in the form of a free base or in the form of pharmaceutically acceptable acid addition salt ranges from 0.05 to 20 mg.

11. The method according to claim 10 wherein the dose unit of 9,10-didehydro-N-methyl-N-(2-propynyl)-6-methyl-8ß-aminomethylergoline in the form of free base or in the form of pharmaceutically acceptable acid addition salt is from 0.1 to 5.0 mg.

12. A pharmaceutical composition for the treatment of cocaine addiction in cocaine addicts comprising from 0.05 to 20 mg of 9,10-didehydro-N-methyl-N-(2-propynyl)-6-methyl-8ß-aminomethylergoline in the form of free base or in the form of pharmaceutically acceptable acid addition salt and a pharmaceutically acceptable carrier.

13. The pharmaceutical composition according to claim 12 comprising from 0.1 to 5.0 mg of 9,10-didehydro-N-methyl-N-(2-propynyl)-6-methyl-8ß-aminomethylergoline in the form of free base or in the form of pharmaceutically acceptable acid addition salt and a pharmaceutically acceptable carrier.

14. The use of 9,10-didehydro-N-methyl-N-(2-propynyl)-6-methyl-8ß-aminomethylergoline in the form of free base or in the form of pharmaceutically acceptable acid addition salt as a partial dopamine agonist for the preparation of the pharmaceutical composition for the treatment of cocaine addiction.